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# GENERAL APPROACH TO THE SYNTHESIS OF POLYQUINANES. PREPARATION OF TRANS, TRANS-4,8-DIACETOXY-TETRACYCLO[9.3.0.0.$^{1,5}$.0$^{7,11}$]TETRADECA-6-ONE VIA THE ALDOL APPROACH.

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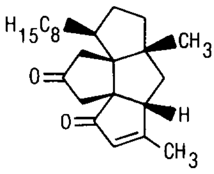
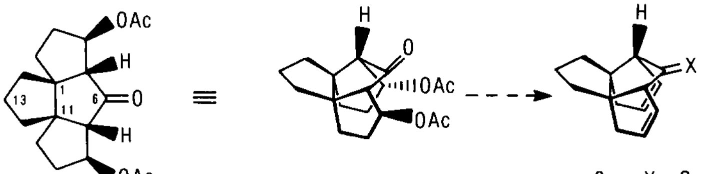
Summary: The synthesis of polyquinane 2 is described. The key steps were the Wolff-Kishner reduction of 8b to provide 10b, and the acetic, sulfuric acid-mediated aldol cyclization to convert the bisacetal 11 into the target 2. Olefin isomerization during the Wolff-Kishner reduction was overcome by addition of $Ag_2CO_3$.



1



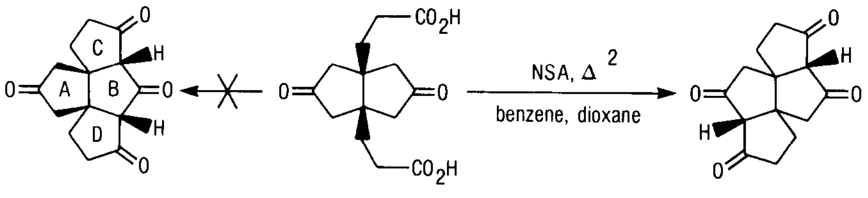
2

3a, X=O
3b, X=$H_2$

Nozoe and Itai reported in 1971 the structure of a novel polyquinane 1, the parent ring system of which is composed of four fused five-membered rings; this diketone 1 arose from a transannular cyclization of ophioboline D[1]. Since we have been interested for some time in a general approach to polyquinanes via the reaction of 1,2-dicarbonyl compounds with dimethyl 3-oxoglutarate,[2] the unusual fusion of the four five-membered rings attracted our attention. We now wish to report the synthesis of trans,trans-4,8-diacetoxy-tetracyclo[9.3.0.0$^{1,5}$.0$^{7,11}$]-tetradeca-6-one 2, the first synthetic compound to contain four five-membered rings joined as in 1. The importance of diacetate 2 goes far beyond the preparation of a new polyquinane ring system. Two of the five-membered rings are held in a disposition such that elimination of the two acetate groups (2 ---> 3a) would provide a diene in which through-space interactions of the olefinic π electrons can be anticipated. Furthermore, the p-orbital of the carbonyl carbon of 3a is orthogonal to those of the diene but would project into the diene system. Comparison of the photoelectron spectrum of 3a with that of 3b would therefore be interesting in regard to the interaction of the electrons in these π orbitals.[3] This possibility provided additional stimulus for the synthesis of a molecule such as 2. Nominally, the generation of four five-membered rings fused as in 2 would be expected to be difficult because of steric interactions between the methylene hydrogens of rings C and D (see 6). This effect was earlier demonstrated in our laboratory[2], since the acid-catalyzed cyclization of diketodiacid 4 (Scheme I) gave tetraone 5 to the complete exclusion of regioisomer 6. The regiospecificity of this reaction was apparently due to the relative strain which results from the three contiguous $sp^2$

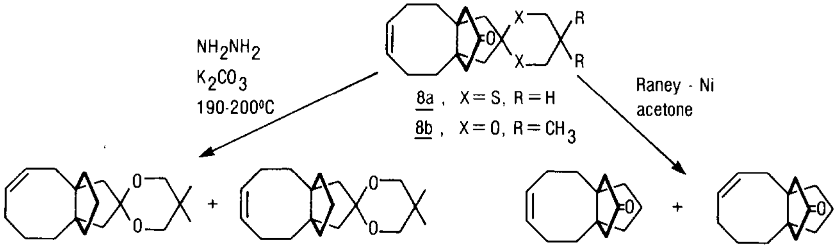
hybridized carbon atoms in 6 coupled with the steric interactions between rings C and D, as alluded to above[2]. In order to overcome these difficulties, it was decided to direct efforts toward construction of 2 via the "aldol approach".[4] In order to direct cyclization toward 2 rather than a derivative of 5, it was necessary to destroy the symmetry of the *cis*-bicyclo[3.3.0]octane-3,7-dione system. For this purpose, the readily available $\Delta^4$-[6.3.3]propellenedione 7[2] was converted into the monothioketal 8a[5] in 70% yield by stirring 7 with 1.2 equivalents of propane-1,3-dithiol at -10°C in a solution of ether-acetic acid (3:2). The low temperature is critical to prevent formation of the bisthioketal of 7; boron-trifluoride etherate served as the catalyst in the usual fashion.[6] It is noteworthy that the 70% yield of crystalline 8a required no recycling of 7, although this process could be performed, if desired. Raney-Nickel mediated desulfurization of monothioketal 8a to provide the desired monoketone 9a proved troublesome. Although a variety of experimental procedures were employed, the best yields (55%) of monoketone were achieved by stirring 8a with a ten-fold excess of deactivated Ra-Ni in refluxing acetone.[7] However, this procedure always gave both the desired monoketone 9a[8] and the $\Delta^3$-olefinic isomer 9b usually in a ratio of 5 to 1 (Scheme II). The separation of the two alkenes 9a and 9b proved to be difficult and the thioketal approach to gram quantities of monoketone 9a was discontinued.

Scheme I



6 , not observed 4 5

Scheme II



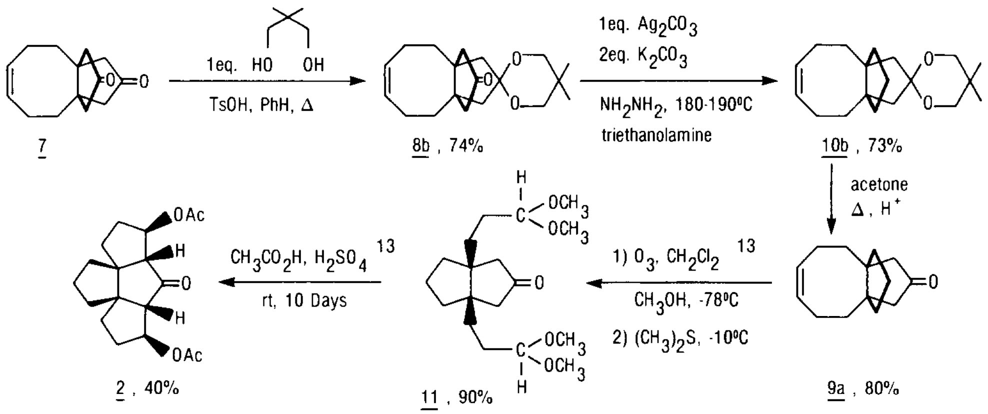
8a , X=S, R=H
8b , X=O, R=$CH_3$

10a 10b 9a 9b

Attempts to convert 7 into a monooxyketal with either ethylene glycol or 1,4-butanediol gave mixtures of starting material, monoketal and bisketal. However, when the [6.3.3]propellenedione 7 (Scheme III) was reacted with one equivalent of 2,2-dimethylpropane-1,3-diol in refluxing benzene in the presence of p-toluenesulfonic acid, good yields of the desired monoketal 8b were obtained. If the reaction was stopped after two hours the ratio of starting dione 7 to monoketal 8b to bisketal was 24:76:0. When the reaction mixture was held at reflux an additional two hours the ratio of 7 to 8b to bisketal [20.5:77:2.5] was not significantly improved. Column chromatography of the reaction mixture on basic alumina provided a 74% yield of the desired crystalline monoketal 8b and 20% recovered starting dione

7. The dione could be recycled, consequently, the selective protection of one of the two symmetrical carbonyl groups of dione 7 had been achieved on a preparative scale. When the monooxyketal 8b was subjected to the conditions of Wolff-Kishner reduction, as well as those of the modified procedure$^{10}$, a 71% yield of the reduction product was obtained; however, this was composed of a mixture of the desired alkene 10b and the $\Delta^3$-isomer 10a, as illustrated in Scheme II. The ratio of 10a to 10b was generally 2:3 but did vary with temperature.$^{11}$

Scheme III



Although it seemed that the isomerization of the double bond in the eight-membered ring of 8b would force us to abandon this approach, an interesting report by Corey et al offered a possible solution.$^{12}$ Silver (I) ion had been successfully employed by these workers to prevent isomerization of olefinic bonds in the oxidative (NBS) removal of 1,3-dithiane protecting groups. In agreement with this observation, Wolff-Kishner reduction of the monoketal 8b, when carried out in the presence of one equivalent of $Ag_2CO_3$, gave a 73% yield of the desired alkene 10b, while less than one percent of the isomeric 10a was observed. The use of silver ion then constitutes a significant improvement in the reduction process and may find applications in other organic reactions where olefin-isomerization represents a problem. Deketalization of 10b occurred in straightforward fashion to provide good yields of the desired [6.3.3] propellene-one 9a.

The monoketone 9a was oxidized with ozone, followed by reductive workup, to provide the bisacetal 11 under conditions analogous to a related transformation carried out in our laboratory.$^{13}$ Moreover the ketal 10b could be converted, in similar fashion, to the related bisacetal in greater than 85% yield. When either the bisacetal 11 or the corresponding bisacetal generated from 10b was treated with acetic acid and a catalytic amount of sulfuric acid ("aldol approach") a 40-45% yield of trans, trans-4,8-diacetoxy-tetracyclo[9.3.0.0$^{1,5}$.0$^{7,11}$ tetradeca-6-one 2 was realized. The yields of 2 from either 11 or from the bisacetal related to 10b were equivalent within experimental error, while the remainder of the material was composed of products of incomplete cyclization.

The elemental analysis, IR and $^{13}$C-NMR spectrum are in agreement with structure 2,$^{14}$ as presented. The stereochemistry of the acetate functions was assigned based upon examination of the proton NMR spectrum. The diacetate 2 contains a plane of symmetry which passes through atoms $C_{(6)}$ and $C_{(13)}$ and also through the midpoint of the $C_{(1)}$-$C_{(11)}$ bond. This is in agreement with the ten-line carbon spectrum obtained for this molecule. In the $^1$H NMR (250 Hz) spectrum of **2** the proton attached to the carbon atom bearing the acetate group appeared at $\delta$5.3 ppm in agreement with the chemical shift observed in the spectrum of related $\beta$-acetoxy ketones.[13,15] The coupling constant between the junction proton and the proton attached to the acetate carbon was found, by double irradiation experiments, to be 1.5 Hz. In keeping with the Karplus relationship of the three-bond coupling constant[16] in related systems[13,15], the small coupling constant (1.5 Hz instead of 9.5 Hz) supports the *trans* configuration of the acetate groups in which the C—O acetate bond is *trans* to the carbon-carbon bond which is attached to the carbonyl group. This *trans*, *trans*-stereochemistry also places the two acetate groups on the convex faces of **2** rather than inside the sterically congested cleft which is formed by the *cis* fusion of three of the five-membered rings. Attempts to convert **2** into **3a**, **3b** and into the parent hydrocarbon will be reported in due course[17].

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5. **8a**, m.p. 84.5-85.5°C; Ir (KBr) 1730.6 cm$^{-1}$; $^1$H NMR(CDCl$_3$) $\delta$1.78-1.67(m,2H), 2.00-2.07 (m,2H), 2.41-2.48(m,4H,J=14.6 Hz), 2.57 (s,4H), 2.65-2.89(m,8H), 2.91-2.97(m,4H), 5.54(t,2H); $^{13}$C NMR(CDCl$_3$) $\delta$ 24.91(t), 29.29(t), 29.57(t), 35.51(t), 50.98(s), 51.53(t), 53.18(s), 58.15(t), 129.23(d), 218.48(s); mass spectrum (CI,CH$_4$) m/e relative intensity 309 (M+1, 100%).
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8. **9a**: colorless oil; Ir(neat) 1734.1 cm$^{-1}$; $^1$H NMR (CDCl$_3$) 2.84(m,10H), 3.06(m,4H), 3.71(m,4H), 6.93(t,2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.16(t), 24.60(s), 35.77(t), 42.21(t), 51.79(t), 52.21(t), 129.82(d), 219(s); mass spectrum (CI,CH$_4$) relative intensity 205 (M+1, 100%). **9b**: $^{13}$C NMR 20.75(t), 26.07(t), 26.71(t), 34.48(s), 38.56(t), 42.09(t), 49.76(t), 50.43(t), 51.07(t), 52.11(t), 52.77(s), 128.67(d), 132.54(d), 219.20(s,C=0); mass spectrum (CI,CH$_4$) relative intensity 205(M+1, 100%).
9. **8b**: mp 64.5-65°C; Ir(KBr) 1739.0ch$^{-1}$; $^1$H NMR(250mHz), CDCl$_3$) $\delta$ 0.88 (s,3H), 1.74-2.42(m, 16H, J=14Hz), 3.38(d,4H), 5.52(t,2H, J=18.6Hz), $^{13}$C NMR (CDCl$_3$) $\delta$ 22.24(q), 24.60(t), 29.80(s), 35.51(t), 50.45(s), 50.76(t), 51.73(t), 71.56(t), 72.15(t), 106.82(s), 129.46(d), 218.57(s); mass spectrum (CI,CH$_4$) m/e (realitive intensity) 305 (M+1, 100%).
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14. **2**: mp 98-99°C; Ir(KBr), 1738.0 and 1724.5 cm$^{-1}$; $^1$H NMR(CDCl$_3$) $\delta$ 1.51-2.20(m,14H), 2.05(s,6H), 2.67(d,2H,J=1.5Hz) 5.28(2H,br t); $^{13}$C NMR (CDCl$_3$) $\delta$ 20.93(q), 24.20(t), 33.34(t), 33.74(t), 42.80(t), 56.03(s), 66.23(d), 76.25(d), 170.06(s), 213.10(s); mass spectrum (EI, 15eV), m/e realitive intensity, 320($M^+$, 3.4%), 260(22.3%), 200(100%).
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17. All compounds gave the expected spectral and elemental analysis. This work was supported by a grant from the National Science Foundation.

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